Approach to a patient with FEVER

DEFINITION OF FEVER

- **Fever is an elevation of body temperature that exceeds the normal daily variation, in conjunction with an increase in hypothalamic set point.**

Hyperpyrexia

- **In the term for an extraordinarily high fever (>41.5°C), which can be observed in patients with severe infections but most commonly occurs in patients with *central nervous system haemorrhages*.**

VARIATION IN TEMPERATURE

- **Normal body temperature ranges from approximately 35.3 to 37.7°C (95.5 to 99.9°F). Body temperature is low in the early morning and high in evening, varying 0.5°C (0.9°F) over the course of the day.**
- **In practice, a general threshold of temperature >37.8°C (100.0°F) or >38°C (100.4°F) is often used.**
- **Anatomic variation.**
- **Physiologic variation:**
  - **Age**
  - **Sex**
  - **Exercise**
  - **Circadian rhythm**
  - **Underlying disorders**

NORMAL BODY TEMPERATURE

- **Maximum normal oral temperature**
  - **At 6 AM : 37.2**
  - **At 4 PM : 37.7**
- **Celsius temperature conversion formulae** from Celsius to Celsius Fahrenheit.
- **[°F] = [°C] × ⁹⁄₅ + 32 [°C] = ([°F] − 32) × ⁵⁄₉ Kelvin**
- **1 °C = 274.15 K = 33.8 °F**

Temperature Classification

- **Normal 36.5–37.5 °C (97.7–99.5 °F).**
- **Hypothermia <35.0 °C (95.0 °F).**
- **Fever/Hyperthermia >37.5–38.3 °C (99.5–100.9 °F).**
- **Hyperpyrexia >40.0–41.5 °C (104–106.7 °F).**

- **For each 1 °C elevation of body temperature:**

A. **Metabolic rate increase 10-15%.**
B. **Insensible water loss increase 300-500ml/m2/day.**
C. **O2 consumption increase 13%.**
D. **Heart rate increase 10-15 bpm/min.**

PHYSIOLOGY OF FEVER

- **Pyrogens:**
  - ***Exogenous pyrogens*:**
    - **Bacteria, Virus, Fungus, Allergen,…**
  - ***Endogenous pyrogen*:**
    - **Immune complex, lymphokine,…**
- **Major En Ps: IL1, TNF, IL6.**

THERMOREGULATION

- **The homeostatic control of body temperature in warm blooded animals is maintained by autonomic, endocrinologic, metabolic and behavioral mechanisms. Body heat is normally generated by cellular metabolism, oxidation of nutrients, circulation of blood and contraction of involuntary muscles. Increased heat can be generated during febrile periods by skeletal muscle contraction (shivering) and increased heat production from the heart, respiratory muscles and brown adipose tissue. Excess heat can be lost by radiation, convection (cutaneous vasodilation) and evaporation (sweating). The neurons of the preoptic region of the anterior hypothalamus are thermosensitive, receiving input from receptors in the skin and core organs and via the mediators transported by the blood.**

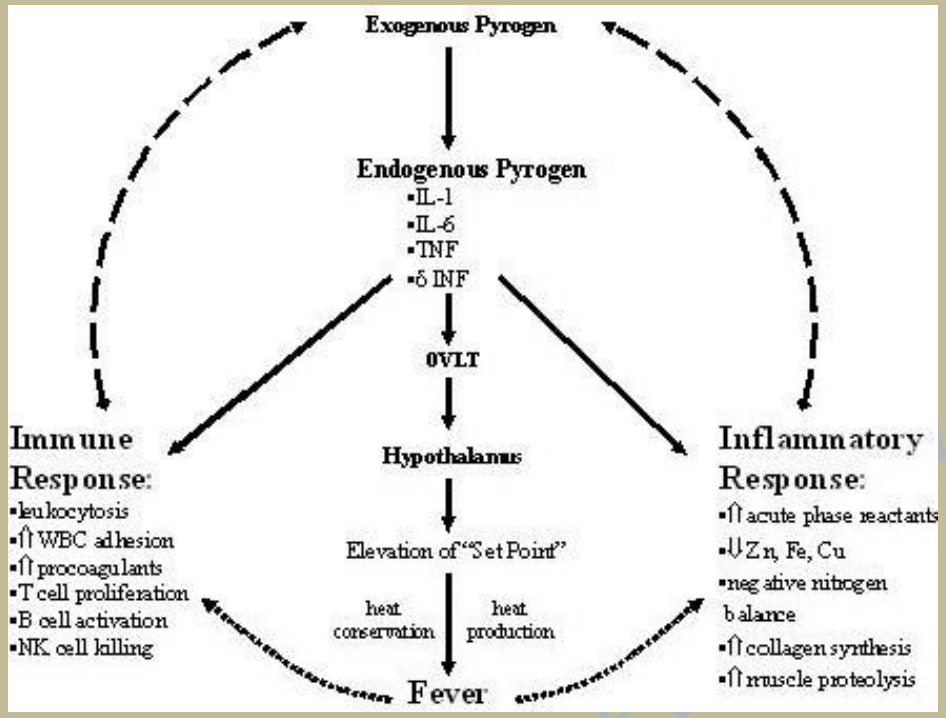
- **When an invasive pathogen is phagocytized, macrophages release endogenous pyrogens that mediate a complex inflammatory and immunologic response. These endogenous pyrogens are most often the lipopolysaccharides of gram negative bacilli and exotoxins and enterotoxins from Streptococci and Staphylococci. See Figure 3. Endogenous pyrogen release can also be caused by non-infectious causes due to antigen-antibody complexes, trauma, complement, androgenic steroid metabolites and bile acids. The endogenous pyrogens, including cytokines such as IL-1, IL-6, TNF-α, ciliary neurotrophic factor and the interferons, act locally and systemically, individually and in combinations, to trigger a large array of metabolic, physiologic and immunologic responses. Table 1 summarizes the effects of IL-1, the most potent of the endogenous pyrogens.**

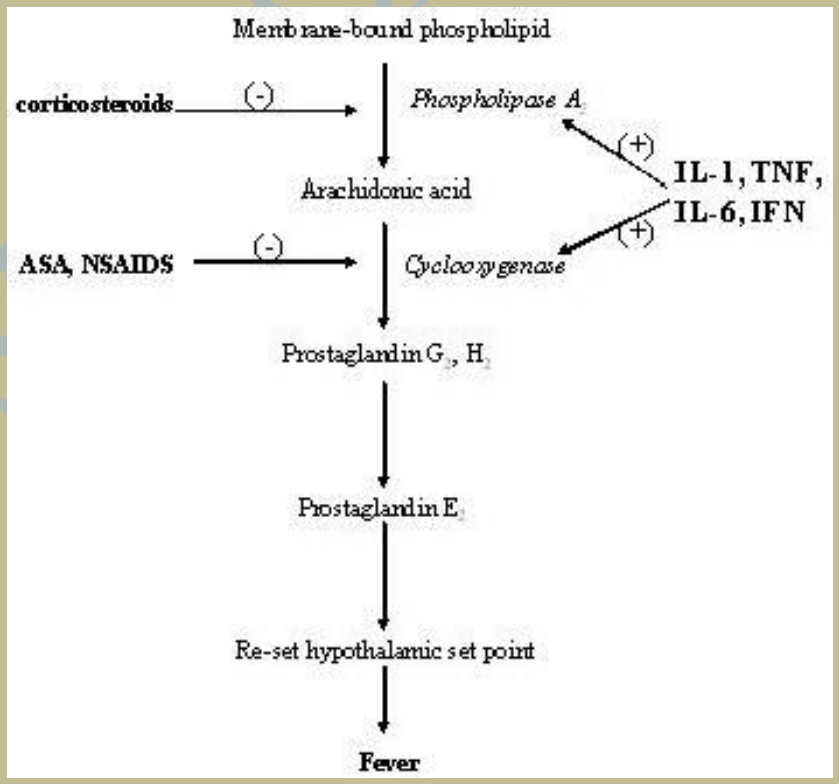
- **In addition, the lipopolysaccharides of gram negative bacilli can directly cause fever, without the induction of endogenous cytokines, by neuronal stimulation of the preoptic area of the anterior hypothalamus. Endogenous antipyretics such as cortisone, cortisol, arginine vasopressin, adrenocorticotropin hormone (ACTH), α melanocyte-stimulating hormone, δ melanocyte-stimulating hormone, and IL-10 protect against the danger of unchecked temperature elevation.**
- **Hormones including glucagon, growth hormone, cortisol, thyroid stimulating hormone, thyroxine, erythropoietin and corticotropin are affected by these cytokines causing increased gluconeogenesis, muscle proteolysis and oxygen and caloric demand. There is increased production of acute phase reactant synthesis such as C-reactive protein, haptoglobin, ceruloplasmin, fibrinogen, ferritin, complement and serum amyloid A.**

- **Concurrently there is a decrease in serum albumin, transferrin, hematocrit, zinc and iron.**
- **Fever is part of this physiologic response to exogenous pyrogen. The cytokines stimulate prostaglandin synthesis in the preoptic areas of the anterior hypothalamus. Since endogenous pyrogens are unable to cross the blood brain barrier, it is felt their effects are mediated via the organum vasculosum of the lamina terminalis, a vascular organ adjacent to the preoptic area. See Figures 2 and 3. Endogenous pyrogen circulating in the organum vasculosum of the lamina terminalis activates phospholipase A2 causing release of membrane bound arachidonic acid.**

- **These cytokines also increase synthesis of cyclooxygenase which catalyzes arachidonic acid to prostaglandin G2 and H2 which serve as the intermediate precursors of prostaglandin E2. See Figure 4. The release of prostaglandin E2 from the hypothalamic endothelium stimulates glial cell prostaglandin E2 receptors which in turn release the neurotransmitter cyclic AMP (cAMP). The elevated cAMP activates the thermoregulatory center to raise the hypothalamic set point. Exogenous pyrogen will also activate Toll-like receptors, type I transmembrane proteins involved in the innate immune system response to infection. The toll-like receptors on the vasculature of the thermoregulatory center stimulate prostaglandin synthesis, to reset the hypothalamic setpoint.**

- **When the hypothalamic setpoint is raised, the body is perceived to be cooler than the new set point. Shivering is initiated to generate heat. Blood is shunted from the periphery to the core to conserve heat and sweating is diminished. The generated heat will raise the body temperature to match the elevated set point. When the hypothalamic set point is lowered, either as part of the normal diurnal fluctuations that occur during an infection or in response to antipyretic agents, heat is lost by evaporation (sweating) and radiation (cutaneous vasodilation). See Figure 1.**


Exogenous Pyrogen
Endogenous Pyrogen
•IL-1
•IL-6
•TNF
•δ INF
OVLT
Hypothalamus
Elevation of "Set Point"
heat conservation
heat production
Fever
Immune Response:
•leukocytosis
•↑ WBC adhesion
•↑ procoagulants
•T cell proliferation
•B cell activation
•NK cell killing
Inflammatory Response:
•↑ acute phase reactants
•↓ Zn, Fe, Cu
•negative nitrogen balance
•↑ collagen synthesis
•↑ muscle proteolysis


Membrane-bound phospholipid
corticosteroids
(-)
Phospholipase A2
(+)
IL-1, TNF, IL-6, IFN
Arachidonic acid
ASA, NSAIDS
(-)
Cyclooxygenase
(+)
Prostaglandin G2, H2
Prostaglandin E2
Re-set hypothalamic set point
Fever

CAUSES OF HYPERTHERMIA SYNDROME

- **Heat stroke: Exercise.**
- **Drug induced:Anticholinergic ‘hypohidrosis’ , Cocaine, ecstasy Amphetamine ,MAO inhibitors.**
- **Neuroleptic malignant syndrome: haloperidol, thiothixene or piperazine, Phenothiazine.**
- **Malignant hyperthermia: Inhalational anaesthetics such as halothane, methoxyflurane, cyclopropane, ethyl ether or muscle relaxants such as succinylcholine.**
- **Endocrinopathy: thyrotoxicosis , pheochromocytoma.**

PUO

- **Classic FUO Fever of unknown origin: is defined as fever higher than 38.3ºC on several occasions lasting for at least three (some use two) weeks without an established etiology despite intensive evaluation and diagnostic testing on 3 outpatient visits, 3 days in the hospital, or 1 week of invasive ambulatory investigation.**

- **Nonclassic FUO is characterized by temperature > 38.3°C recorded on multiple occasions with no clear etiology after at least 2 days of culture incubation in addition the following specific features:**

A. Neutropenic FUO (immunodeficient FUO): neutrophil count of < 500/mm^3 or an anticipated fall in neutrophil count to < 500/mm^3 within 1–2 days.

B. HIV-associated FUO: fever that lasts for > 4 weeks (or > 3 days if hospitalized) in a patient with HIV.

C. Nosocomial FUO: fever that lasts for > 3 days in a hospitalized patient who was afebrile on admission.

Categories of classic FUO [1][3][4][5]

Category [1]	Common causes	Less common causes

Infection (11–55%)	• Tuberculosis
	• Brucellosis
	• Q fever
	• Subacute bacterial endocarditis
	• Complicated UTI
	• Abscess
		• Infrequent
		  ◦ Typhoid fever
		  ◦ Toxoplasmosis
		  ◦ Cat scratch disease
		  ◦ Extrapulmonary tuberculosis
		  ◦ Viral infection (e.g., EBV, CMV, HIV)
		• Rare
		  ◦ Leptospirosis
		  ◦ Periapical dental abscess
		  ◦ Chronic sinusitis
		  ◦ Mastoiditis
		  ◦ Vertebral osteomyelitis
		  ◦ Tick-borne diseases
		  ◦ Chronic prostatitis
		  ◦ Recurrent cholangitis
		  ◦ Whipple disease
		  ◦ Parasitic infections (e.g., malaria, visceral leishmaniasis)
		  ◦ Fungal infections (e.g., histoplasmosis, coccidioidomycosis)

Inflammatory or rheumatic conditions (12–34%)	• Adult-onset Still disease
	• Temporal arteritis
		• Infrequent
		  ◦ SLE
		  ◦ Systemic vasculitis: e.g, polyarteritis nodosa
		• Rare
		  ◦ Takayasu arteritis
		  ◦ Kikuchi disease
		  ◦ Behcet disease
		  ◦ Gout or pseudogout
		  ◦ Felty syndrome

Malignancy (7–35%) [6][1]	• Hodgkin lymphoma • Non-Hodgkin lymphoma • Leukemia • Renal cell carcinoma • Melanoma	• Castleman disease • Atrial myxoma • Colonic adenocarcinoma • Multiple myeloma

Miscellaneous (2–20%)	• Drug fever
	• Cirrhosis
	• Postmyocardial infarction syndrome
	• Stroke
		• Infrequent
		  ◦ Subacute thyroiditis
		  ◦ Inflammatory bowel disease
		  ◦ Sarcoidosis
		• Rare
		  ◦ Pulmonary embolism
		  ◦ Familial periodic fever syndromes: e.g., familial Mediterranean fever
		  ◦ Cyclic neutropenia
		  ◦ Factitious fever

TREATMENT OF FEVER

- **Reasons not to treat fever:**
  - **The growth and virulance of some organisms**
  - **Host defense-related response**
  - **Fever is an indicator of disease**
  - **Adverse effect of antipyretic drugs**
  - **Iatrogenic stress**
  - **Social benefits**

TREATMENT OF FEVER

- **Reasons to treat fever:**
  - **The elderly individual with pulmonary or cardiovascular disease.**
  - **The patient at additional risk from the hypercatabolic state (Poor nutrition, Dehydration).**
  - **The young child with a history of febrile convulsions.**
  - **Toxic encephalopathy or delirium.**
  - **Pregnant women (contraversy).**
  - **For the patient comfort.**
  - **Hyperpyrexia.**

Mechanisms of Antipyretic Agents

- The synthesis of PGE2 depends on the constitutively expressed enzyme cyclooxygenase. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE2.
- Inhibitors of cyclooxygenase are potent antipyretics.
- There are four receptors for PGE2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever.
- Although PGE2 is essential for fever, it is not a NT.
- Rather, the release of PGE2 from the brain side of the hypothalamic endothelium triggers the PGE2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine (cyclic AMP), which is a neurotransmitter.

- ***Acetaminophen*** **is a poor cyclooxygenase inhibitor in peripheral tissue and is without noteworthy anti-inflammatory activity; in the brain, however, acetaminophen is oxidized by the p450 cytochrome system, and the oxidized form inhibits cyclooxygenase activity.**
- ***Oral aspirin*** **and acetaminophen are equally effective in reducing fever in humans. Nonsteroidal anti-inflammatory agents (NSAIDs) such as indomethacin and ibuprofen are also excellent antipyretics.**
- **Chronic high-dose therapy with antipyretics such as aspirin or the NSAIDs used in arthritis does not reduce normal core body temperature.**

- **Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and the gastrointestinal tract.**
- **Therefore, acetaminophen is preferred to all of these agents as an antipyretic.**
- **In children, acetaminophen must be used because aspirin increases the risk of Reye's syndrome.**

- **Don’t give aspirin to children under 18 years (Reye’s Syndrome)due to the possibility of damage to cellular mitochondria.**

- ***Glucocorticoids*** **act at two levels.**
- ***First*****, similar to the cyclooxygenase inhibitors, glucocorticoids reduce PGE2 synthesis by inhibiting the activity of phospholipase A2 , which is needed to release arachidonic acid from the cell membrane.**
- ***Second*****, glucocorticoids block the transcription of the mRNA for the pyrogenic cytokines.**

- **Drugs that interfere with vasoconstriction (*phenothiazines*, for example) can act as antipyretics, as can drugs that block muscle contractions.**
- **However, these agents are not true antipyretics since they *can also reduce core temperature independently of hypothalamic control.***

- **The use of cooling blankets facilitates the reduction of temperature; however, cooling blankets should not be used without oral ntipyretics, (hyperpyrexia).**
- **In hyperpyretic patients with central nervous system disease or trauma, reducing core temperature mitigates the ill effects of high temperature on the brain.**
- **Physical cooling with sponging, fans, cooling blankets, and even ice baths should be initiated immediately in conjunction with the administration of intravenous fluids.**
- **internal cooling can be achieved by gastric or peritoneal lavage with iced saline.**
- **hemodialysis or even cardiopulmonary bypass with cooling of blood may be performed.**

Malignant hyperthermia

- **An inherited abnormality of skeletal-muscle *sarcoplasmic reticulum* that causes a rapid increase in intracellular calcium levels in response to halothane and other inhalational anaesthetics or to succinylcholine.**
- **Elevated *temperature*, *increased muscle metabolism* 'elevated serum CK' , rigidity , rhabdomyolysis, acidosis , and cardiovascular instability develop rapidly.**
- **This condition is often fatal.**
- **Should be treated immediately with cessation of anesthesia and intravenous administration of dantrolene sodium.**
- **Procainamide should also be administered to patients with malignant hyperthermia because of the likelihood of ventricular fibrillation in this syndrome.**

The neuroleptic malignant syndrome

- **Can occur with phenothiazines and other drugs such as haloperidol and is characterized by muscle rigidity, autonomic dysregulation, and hyperthermia.**
- **This disorder appears to be caused by the *inhibition of central dopamine receptors in the hypothalamus*, which results in increased heat generation and decreased heat dissipation.**

- ***Dantrolene*** **is indicated in the neuroleptic malignant syndrome and in drug-induced hyperthermia and may even be useful in the hyperthermia of thyrotoxicosis.**
- **The neuroleptic malignant syndrome may also be treated with *bromocriptine, levodopa, amantadine, or nifedipine* or by induction of muscle paralysis with *curare and pancuronium.***
- **Tricyclic antidepressant overdose may be treated with *physostigmine.***

Measuring sites of Temp.

- Temperature in the mouth (oral) is at or over 37.7 °C.
- Temperature in the anus (rectal) is at or over 37.5–38.3 °C.
- The rectal temperature is 0.3°C to 0.6°C, higher than the oral temperature.
- Temperature under the arm (axillary) or in the ear (otic) is at or over 37.2 °C.
- Axillary temperature is 0.3°C to 0.6°C, lower than the oral temperature.

What is the difference between hyperthermia and hyperpyrexia?

- **In hyperpyrexia the body's temperature regulation mechanism sets the body temperature above the normal temperature, then generates heat to achieve this temperature, while in hyperthermia the body temperature rises above its set point due to an outside source.**

ATTENUETED FEVER RESPONSE

- **Fever may not be present despite infection in:**
  - **Newborn**
  - **Elderly**
  - **Uremia**
  - **Significant malnourished individual**
  - **Taking corticosteroids**

DRUG FEVER

- **Pathogenesis:**

A. **Contamination of the drug with a pyrogen or microorganism.**

B. **Pharmacologic action of the drug itself.**

C. **Allergic (hypersensitivity) reaction to the drug.**

- **Onset and duration:**

D. **Onset: 1-3 weeks after the start of therapy.**

E. **Duration: remits 2-3 days after therapy is stoped.**

APPROACH TO THE PATIENT WITH FEVER

ACUTE FEBRILE ILLNESS

APPROACH TO FEVER

- **Personal History:**
  - **Age & sex.**
  - **Occupation.**
  - **Place of origin ‘nationality & address’ , Travel History.**
  - **Habits & Hobbits**
    - **Sexual Practices.**
    - **Injection Drug Abuse.**
    - **Excessive Alcohol Use & smoking.**
    - **Consumption of Unpasteurized Dairy Products.**

APPROACH TO FEVER

- **Past medical & surgical Hx:**
  - **Previous blood products transfusion/dialysis.**
  - **Vaccination Hx.**
  - **Chronic Diseases:**
    - **Cirrhosis.**
    - **Chronic Heart Diseases.**
    - **Chronic Lung Diseases.**
    - **Chronic kidney disease.**
  - **Immunodeficiency.**
  - **Splenectomy.**
  - **Surgical Implantation of Prosthesis.**

APPROACH TO FEVER

- **Drug History:**
  - **Antipyretics.**
  - **Immunosuppressants ‘glucocorticoids/chemotherapy’.**
  - **Antibiotics.**
- **Family History:**
  - **TB in the Family.**
  - **Recent Infection in the Family.**
  - **Hx of cancers.**

APPROACH TO FEVER

- **Associated Symptoms:**
  - **Shaking , chills ,shivering , rigors.**
  - **Ear pain, Ear drainage, Hearing loss.**
  - **Visual and Eye Symptoms.**
  - **Sore Throat, dysphonia or dysphagia.**
  - **Chest and Pulmonary Symptoms.**
  - **Abdominal Symptoms.**
  - **Back pain, Joint or Skeletal pain.**
  - **Meningismus/ Focal neurological deficits.**

Types of fever	Course	Examples of associated conditions
Continuous		• Viral and bacterial infections
Remittent		• Viral infections • Acute bacterial endocarditis
Intermittent		• Pyogenic, focal infections • Tuberculosis • Juvenile idiopathic arthritis
Undulant		• Brucellosis
Biphasic		• Dengue fever
Recurrent		• Tick-borne diseases (e.g., borreliosis) • Hodgkin lymphoma

PATTERN OF FEVER

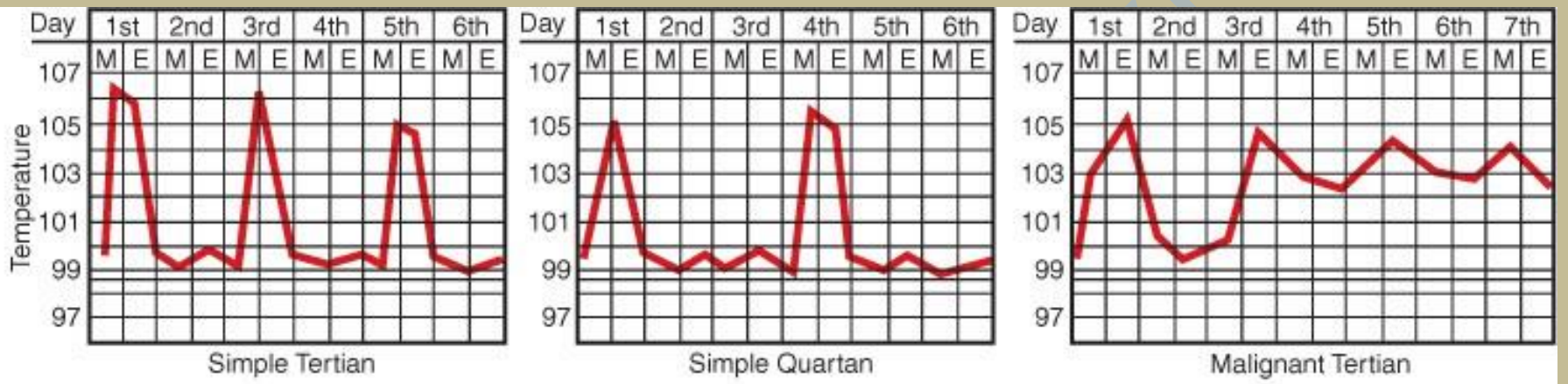
- **Sustained (Continuous) Fever.**
- **Remittent Fever.**
- **Intermittent Fever (Hectic Fever).**
- **Relapsing Fever: Days of Fever Followed by a Several Days Afebrile , examples:**
  - **Tertian Fever**
  - **Quartan Fever**
  - **Pel Ebstein Fever**
  - **Fever Every 21 Day**

- ***Pel-Ebstein fever*, with fevers lasting 3 to 10 days followed by afebrile periods of 3 to 10 days, is classic for *Hodgkin's lymphoma.***
- **Ddx of Fever and rigor: Flu , Brucellosis , Abscess , Pharyngitis , Malaria.**
- **Ddx of Fever and wight loss: TB , malignant disease.**

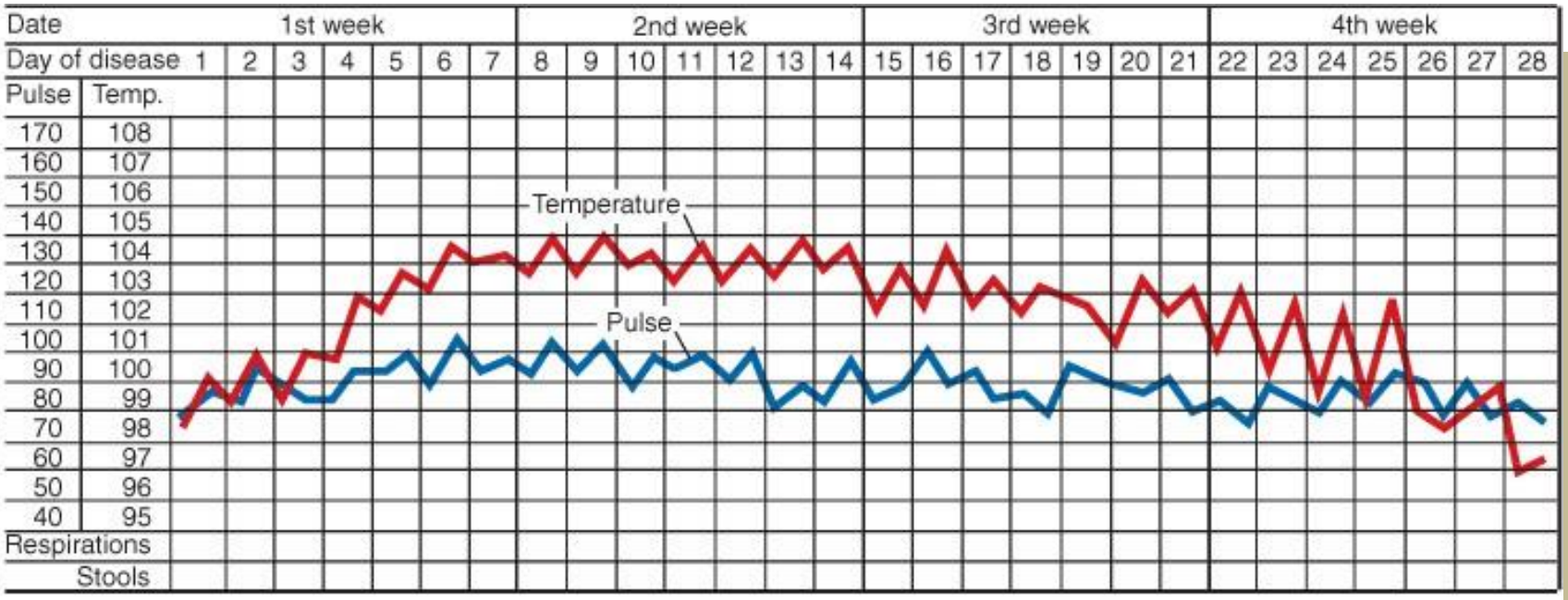
Fever + headche + dec level of contiousness = encephalitis.

Without any change in the level of contiousness = meningitis.

A


Day
1st
2nd
3rd
4th
5th
6th
7th
M E
Temperature
107
105
103
101
99
97
Simple Tertian
Simple Quartan
Malignant Tertian

B


Date
1st week
2nd week
3rd week
4th week
Day of disease 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Pulse
Temp.
170 108
160 107
150 106
140 105
130 104
120 103
110 102
100 101
90 100
80 99
70 98
60 97
50 96
40 95
Respirations
Stools
Temperature
Pulse

APPROACH TO FEVER

- **Physical Examination:**
  - **Vital Signs**
  - **Neurological Exam.**
  - **Skin Lesions,Mucous Membrane**
  - **Eyes**
  - **ENT**
  - **Lymphadenopathy**
  - **Lungs and Heart**
  - **Abdominal Region (Hepatomegaly,Splenomegaly)**
  - **Musculoskeletal**

LABORATORY STUDY IN PATIENT WITH FEBRILE ILLNESS

- **Assess the extent and severity of the inflammatory response to infection**
- **Determine the site(s) and complications of organ involvement by the process**
- **Determine the etiology of the infectious disease**

Initial diagnostics [2][1][7][12][3]

Minimum diagnostic workup

- **Laboratory studies**
  - CBC with differential (see "Differential diagnoses of fever by associated finding" and "Overview of WBC parameters")
  - Acute phase reactants: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
  - Liver chemistries
  - Serum electrolytes
  - LDH
  - Creatine kinase
  - Urinalysis and urine culture
  - Blood culture (three sets) if bacteremia is suspected [8][3]
- **Imaging**
  - X-ray or CT chest
  - Ultrasound or CT abdomen and pelvis

Targeted testing based on diagnostic clues [3][9][2][1]

Category		Diagnostic clues	Suggested testing
Infection		• Chills • History of recent travel • Recent invasive procedure and/or presence of an implant • History of animal contact • History of tuberculosis (exposure or previous infection) • Immunocompromised state • Elevated procalcitonin	• Tests to identify the underlying source; for example: ◦ Microbiology ▪ Consider repeating blood and urine cultures. ▪ CSF culture, if indicated ◦ Serology ▪ HIV serology ▪ Hepatitis A, B, and E serology ◦ Tuberculosis testing ▪ PPD skin test ▪ Tuberculosis IFN-γ release assays ◦ Endocarditis testing ▪ Consider echocardiography. ▪ Modified Duke criteria to supplement clinical findings
Inflammatory disease		• Prominent arthralgia or arthritis • Prominent myalgia	• Creatine kinase • Antinuclear antibodies • Rheumatoid factor • Antineutrophil cytoplasmic antibodies (ANCA) [13]
Malignancy		• Clinically significant unintentional weight loss • Early anorexia • Other B-symptoms • Pruritus after a hot bath [14] • Positive naproxen test • History of malignancy • Immature cells on CBC and peripheral blood smear • Elevated LDH	• Usual recommended age-based cancer screening if not already performed [7] ◦ Cervical cancer screening ◦ Colon cancer screening ◦ Lung cancer screening ◦ Breast cancer screening ◦ Prostate cancer screening
Miscellaneous	**Subacute thyroiditis**	• Signs of thyrotoxicosis • Neck or jaw pain	• Thyroid function tests • Thyroid antibodies
	Thromboembolic disease	• Leg pain or swelling • Dyspnea • Chest pain • Risk factors for VTE (including history of long-distance travel)	• D-dimer • Determine the pretest probability of VTE. ◦ See "Wells criteria for DVT." ◦ See "Wells criteria for PE." • Perform further diagnostics accordingly. ◦ See "Diagnostic approach to suspected lower-extremity DVT." ◦ See "Diagnostic approach to suspected PE."
	Cirrhosis	• Jaundice • Splenomegaly • Altered liver chemistries • Ascites	• See "Diagnostics for liver cirrhosis."
	Sarcoidosis	• Pulmonary symptoms: e.g., dyspnea, cough • Extrapulmonary manifestations: e.g., arthritis, uveitis, erythema nodosum [15]	• X-ray or CT chest (if not already performed) • See "Diagnostics for sarcoidosis."
	Drug fever	• Fever coincides with the administration of a drug • Can be associated with rash (e.g., morbilliform drug eruption)	• Stop nonessential drugs. • Fever usually resolves within 72 hours of stopping the drug [12]
	Familial Mediterranean fever [16]	• Episodic fever • Painful polyserositis (e.g., abdominal pain, arthralgia, chest pain) • Erysipelas-like rash (uncommon)	• Clinical diagnosis • Consider genetic testing for mutations in the MEFV gene.

Advanced diagnostics

If the underlying etiology remains undiagnosed despite initial diagnostics, advanced diagnostics to evaluate for less common causes of FUO should be performed.

- **Additional nonspecific laboratory studies**
  - Serum ferritin: Highly elevated levels are suggestive of a noninfectious etiology. [17][7]
  - Cryoglobulins: may be positive in patients with neoplastic disease, inflammatory disease, or viral infection
  - Cold agglutinins: elevated in certain infections (e.g., mycoplasma pneumonia, EBV, viral hepatitis), malignancy (e.g., lymphoma), or inflammatory disease
  - Uric acid: elevated levels are suggestive of malignancy
- **Further serologic testing**, e.g., for EBV infection, CMV infection, brucellosis, bartonellosis
- **Serum protein electrophoresis** [3]
  - Monoclonal gammopathy: e.g., multiple myeloma, Waldenstrom macroglobulinemia
  - Polyclonal gammopathy: e.g., HIV, malaria, SLE
- **Advanced imaging studies**
  - **FDG-PET scan** [18][19]
    - Consider for all patients without a diagnosis after initial diagnostics, especially those with elevated CRP and/or ESR. [7]
    - FDG uptake identifies tissues with high metabolic activity, indicating areas that warrant further investigation.
  - CT or MRI chest and abdomen: Consider if not already obtained, FDG-PET is unavailable, or FDG-PET indicates an intrathoracic or intraabdominal abnormality. [20][3]
  - Transesophageal echocardiogram (TEE): Consider for suspected bacterial endocarditis. [21][22]
- **Invasive tests** [2][23]
  - Lymph node biopsy [3]
    - Consider for patients with lymphadenopathy.
    - Posterior cervical, supra/infraclavicular, and epitrochlear nodes have the highest diagnostic yield.
    - Avoid anterior cervical, axillary, and inguinal node biopsies, as histological results are usually nondiagnostic.
  - Temporal artery biopsy: Consider in patients ≥ 55 years of age. [8][7]
  - Liver biopsy: Consider in patients with suspected hepatic involvement (e.g., those with altered liver enzymes or liver abnormalities on imaging studies). [7]
  - Bone marrow studies
    - Consider bone marrow biopsy if diagnostic clues for myeloproliferative or myelodysplastic disease are present (e.g., pancytopenia, atypical cells on peripheral blood smear). [7]
    - Consider bone marrow culture for suspected culture-negative bacterial endocarditis, miliary tuberculosis, or typhoid fever if it would alter the management. [3][12]

INDICATIONS OF HOSPITALISATION IN PATIENT WITH FEBRILE ILLNESS

- **Persons who are clinically unstable or are at risk for rapid deterioration**
- **Major alterations of immunity**
- **Need for IV Antimicrobials or other fluids**
- **Advanced age**